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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/599,346	09/26/2006	Gianpaolo Bravi	PB60786USW	7196

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EXAMINER	
COPPINS, JANET L	
ART UNIT	PAPER NUMBER
1626	

NOTIFICATION DATE	DELIVERY MODE
04/02/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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Office Action Summary	Application No.	Applicant(s)	
	10/599,346	BRAVI ET AL.	
	Examiner	Art Unit	
	JANET L. COPPINS	1626	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 April 2007*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-5,9,10,14 and 15* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *1,2,9 and 10* is/are allowed.

6)☒ Claim(s) *3-5,14 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/26/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Claims 1-5, 9, 10, 14 and 15 are currently pending in the instant application.

Priority

2. The instant application is a 371 of PCT/GB2005/001071, filed March 22, 2005 which claims priority from GB 0406916.7 filed March 26, 2004; GB 0406918.3 filed March 26, 2004; GB 0423000.9 filed October 15, 2004; and GB 0423001.7 filed October 15, 2004.

Information Disclosure Statement

3. Applicants' Information Disclosure Statement, IDS, submitted September 26, 2006, has been considered by the Examiner. Please refer to the signed copy of Applicants' PTO-1449 form, submitted herewith.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 3-5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement, regarding the treatment or prevention of viral infection.

In *In re Wands*, 8 USPQ2d 1400 (1988), factors to be considered in determining whether a disclosure meets the enablement requirement of 35 U.S.C. § 112, first paragraph, have been described. They are:

1. the nature of the invention,
2. the state of the prior art,
3. the predictability or lack thereof in the art,
4. the amount of direction or guidance present,
5. the presence or absence of working examples,
6. the breadth of the claims,
7. the quantity of experimentation needed, and

8. the level of the skill in the art.

The nature of the invention

The nature of the invention is the treatment or prevention of viral infection in a subject in need thereof (claims 3 and 5) and treating or preventing HCV infection (claim 4).

The state of the prior art and the predictability or lack thereof in the art

The state of the prior art is that the pharmacological art involves screening *in vitro and in vivo* to determine which compounds exhibit the desired pharmacological activities (i.e. what compounds can treat which specific diseases by what mechanism). There is no absolute predictability even in view of the seemingly high level of skill in the art. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting any therapeutic regimen on its face.

It is noted that the pharmaceutical art is unpredictable, requiring each embodiment to be individually assessed for physiological activity. *In re Fisher*, 427 F.2d 833, 166 USPQ 18 (CCPA 1970) indicates that the more unpredictable an area is, the more specific enablement is necessary in order to satisfy the statute. In the instant case, the claimed invention (i.e. treating or preventing *any* or *all* viral infections, or *preventing* HCV infection) is highly unpredictable since one skilled in the art would recognize that in regards to therapeutic effects of the above listed viral infections, whether or not a specific viral disease is effected by the inhibition of HCV polymerase would make a difference. Applicants claims encompass a method of treating or preventing *any* or *all* viral infections, as well as treating or *preventing* HCV, by administering a compound of Formula (I). As such, the specification fails to enable the skilled artisan to use the instant claimed compounds to treat *any* viral infections, other than HCV. The specification also

fails to enable one skilled in the art to use the claimed compounds to **prevent** *any* viral infection. In addition, there is no proof that the claimed compounds have ever been administered to a human or to an animal model.

Currently, Antiviral drugs are currently only effective against a few viral diseases, such as influenza, herpes, hepatitis B and HIV. The obstacles to therapeutic approaches and vaccine development with regard to retroviruses associated with hepatitis in humans are well documented in the literature. See, for example The Centers for Disease Control: Hepatitis C, (http://www.cdc.gov/hepatitis/HepatitisC.htm):

> "Hepatitis C is a contagious liver disease that results from infection with the hepatitis C virus. It can range in severity from a mild illness lasting a few weeks to a serious, lifelong illness. Hepatitis C is usually spread when blood from a person infected with the hepatitis C virus enters the body of someone who is not infected. Most people become infected with the hepatitis C virus by sharing needles or other equipment to inject drugs.
>
> Hepatitis C can be either "acute" or "chronic." Acute hepatitis C virus infection is a short-term illness that occurs within the first 6 months after someone is exposed to the hepatitis C virus. For most people, acute infection leads to chronic infection. Chronic hepatitis C is a serious disease than can result in long-term health problems, or even death.
>
> There is no vaccine for hepatitis C."

These obstacles include and are not limited to : 1) the extensive genomic diversity associated with hepatitis, particularly with respect to the gene encoding the envelope protein, 2) the fact that the modes of viral transmission include virus-infected mononuclear cells, which pass the infecting virus to other cells in a convert form, as well as via free virus transmission, 3)

existence of a latent form of the virus, 4) the ability of the retrovirus to traverse the blood brain barrier and 5) the complexity and variation of the elaboration of the disease. The existence of these obstacles establishes that the contemporary knowledge in the art would prevent one of ordinary skill in the art from accepting therapeutic regimen on its face. In addition, there is no established correlation between *in vitro* activity and accomplishing "prevention" of viral infections, especially HCV infections, *in vivo*, and those skilled in the art would not accept allegations in the instant specification to be reliable predictors of success. A person skilled in the art would not be able to use the instant compounds to treat or **prevent** viral infections as claimed, including HCV, since there is no description of an actual method wherein any viral infection in a host is p**revented**.

Hence, in the absence of a showing of correlation between all of the viral infections encompassed by claim 3, as capable of treatment by the inhibition of HCV polymerase, one of skill in the art is unable to fully predict possible results from the administration of the compound of the claims to treat *any* or *all* viral infections, which would include such difficult and diverse viral infections to be treated such as Adenoviruses, Enteroviruses, Rhinoviruses, Influenza, Rubella, Epstein-Barr, mononucleosis, herpesviruses, Cytomegalovirus, HIV and AIDS, etc. Furthermore, hepatitis viruses such as HCV are known to have many obstacles that would prevent one of ordinary skill in the art from accepting "prevention" on its face.

The amount of direction or guidance present and

the presence or absence of working examples

The only direction or guidance present in the instant specification is the *in vitro* binding assay found on pages 121-123 of the Specification, in which the instant compounds are shown to

inhibit wildtype HCV polymerase activity. There are no working examples present for the treatment or prevention of any viral infection, or the prevention of HCV infection.

The breadth of the claims

The breadth of the claims is the treatment or prevention of *any* viral infection, or the treatment or prevention of HCV infection, with a compound of the instant claims. There are thousands of known viral infections, that can affect the nose, throat, upper airways, skin, blood, etc including those discussed above, i.e. Adenoviruses, Enteroviruses, Rhinoviruses, Influenza, Rubella, Epstein-Barr, mononucleosis, herpesviruses, Cytomegalovirus, HIV and AIDS, etc.

The quantity of experimentation needed

The quantity of experimentation needed is undue experimentation. One of skill in the art would need to determine which viral infections would be benefited (treated or **prevented**) by the inhibition of HCV polymerase and would furthermore then have to determine which of the claimed compounds would provide **prevention** of HCV infection, if any.

The level of the skill in the art

Those practitioners who treat viral infections of any type (medical clinicians, pharmacists and/or pharmaceutical chemists) presumably would be highly skilled in the art.

However, due to the unpredictability in the pharmaceutical art, it is noted that each embodiment of the invention is required to be individually assessed for physiological activity by *in vitro* and *in vivo* screening to determine which compounds exhibit the desired pharmacological activity and which diseases would benefit from this activity.

Thus, the specification fails to provide sufficient support of the broad use of the compound of the instant claims for the treatment or prevention of any viral infection, or the

prevention of HCV infection. As a result, necessitating one of skill to perform an exhaustive search for which diseases can be treated by what compounds of the instant claims in order to practice the claimed invention. Genentech Inc. v. Novo Nordisk A/S (CA FC) 42 USPQ2d 1001, states that" a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion" and "[p]atent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable".

Therefore, in view of the Wands factors and *In re Fisher* (CCPA 1970) discussed above, to practice the claimed invention herein, a person of skill in the art would have to engage in undue experimentation to test which viral infections can be treated or prevented by the compound encompassed in the instant claims, or whether the instant compound would in fact prevent HCV infection, with no assurance of success.

This rejection can be overcome by combining claims 3 and 4, and deleting any "prevention" language from the claim, such that claim 3 is directed to a method of treating HCV infection.

6. The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

7. Claims 14 and 15 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Both claims recite the limitation, "A pharmaceutical composition according to claim 9..." however there is insufficient antecedent basis for this limitation in the claims. Claim 9 is directed to a "pharmaceutical formulation," not a composition. This rejection can be overcome by amending claim 9 to recite a pharmaceutical composition.

Conclusion

8. In conclusion, claims 1-5, 9, 10, 14 and 15 are currently pending in the instant application, claims 3-5, 14 and 15 are currently rejected, and the remaining claims appear allowable over the prior art.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JANET L. COPPINS whose telephone number is (571)272-0680. The examiner can normally be reached on M-F 8:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Joseph K. McKane can be reached on 571.272.0699. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/REI-TSANG SHIAO /

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March 19, 2009

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